Pharmacy Focus:
Dissecting Gene Therapies

Before the Food and Drug Administration (FDA) approves any product, including a gene therapy, researchers must conduct preclinical studies. These studies test gene therapies in a laboratory on non-animal study subjects. The manufacturer must then submit an application to the FDA, and upon approval, the manufacturer may begin clinical trials.

Clinical trials usually occur in three phases:

- **Phase 1** of a trial is conducted in a small group of participants, mainly focusing on safety, the dose and dosing schedule and the administration of the product
- **Phase 2** trials expand the participant group, now focusing on the efficacy of the test drug
- **Phase 3** trials are conducted on an even larger group of people with the disease, and once these phases are complete, the product will be approved for market use; however, the product and the participants continue to be monitored for several years after approval.[1]

Efficacy Challenges

Gene therapies are breakthrough treatments for rare diseases. They make it an exciting time in medicine, but they also present important limitations that should be noted:

- These therapies are not proving to be curative
- They are used to slow the progression or severity of a disease for some amount of time
- Time will play an important role in gathering and interpreting data that helps in the creation of future gene therapies

Efficacy is a product's ability to produce the desired or intended result. In drug/therapy research settings, it refers to the ability to achieve the maximum response, and in clinical settings, it is the ability to make a beneficial change/have the intended therapeutic effect.

The following shares some of the findings and challenges we have seen with early gene and cell therapies, as claims data has increased over the past four years:

Luxturna® (voretigene neparvovec-rzyl) entered the market in 2017 as a gene therapy treatment for a gene-specific type of retinal dystrophy (blindness). With Luxturna® marketed for use, an otherwise inexpensive disease state received an $850,000 option with ambitions to increase visual acuity (a person's ability to discern the shapes and details of the things they see). During clinical trials, traditional visual acuity testing did not yield significant endpoints, and as a response, the manufacturer developed its own scale for outcomes.[2]

At HM Insurance Group, we have not seen many claims for Luxturna® to date. However, we have found ongoing monitoring for some adverse effects like glaucoma and cataracts associated with the intra-ocular injection in those who have received Luxturna®. This was part of the initial realization that the success of gene therapies is not only dependent upon the genetic mutation, but also in relation to the severity of the disease, the length of time from treatment and the adverse events the patient experiences. The current FDA approval pipeline includes additional gene therapies for specific visual diseases.

CAR T-cell therapies also were launched in 2017 with the approval of Kymriah®. These therapies are indicated for non-solid tumor cancers. The prices are set by the manufacturers like all other marketed products; however, because they are IV infusions, they are administered by a provider, which impacts the total cost of the treatment. To attain appropriate reimbursement, it is safe to assume the provider will be billing cellular therapies at a significantly higher price than what was established by the manufacturer. Ancillary services may double or triple the total amount anticipated for the cellular therapy.

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Efficacy Challenges, *continued*

Today, there are five CAR T-cell therapies approved by the FDA, and they have been approved for expanded use to treat several different types of cancers. Some initial data submitted to the FDA indicated that the immediate response rate was promising, but during follow-up, that rate fell significantly, with cancer activity recurring in a large majority of patients.[3] Many patients also went on to require clinical interventions, including clinical trials for additional CAR T-cell therapy and bone marrow transplants. Others have died.[4]

The data from the clinical trials is reflected in the claims activity we have seen at HM Insurance Group. We have experience in dozens of cellular therapies to date, not only in the identification of the claim, but also in the management and strategies associated with some of the long-term effects. CAR T-cell therapies result in various interventions before and after the one-time infusion, and ancillary claims are seen between $400,000 to $1,600,000.

At HM Insurance Group, we assess cost containment strategies to avoid unexpected high-cost claims. This is important as there are second generation CAR T-cell therapies entering the market. Manufacturers also are evaluating CAR T-cell therapies for utilization earlier on in disease progression. Once approved, these updates will result in less CAR T-cell clinical trials (moving the CAR T-cell cost onto the Health Plan) and many more options for high-cost claims around cellular therapy and the corresponding ancillary expenses.

Zolgensma® has been used since market approval in 2019 for infants and children under the age of two, who are diagnosed with spinal muscular atrophy (SMA) type 1 and type 2. Since the approval of Zolgensma®, HM has supported cost containment efforts for more than a dozen treatments nationally. Ongoing monitoring has shown that within our own book, nearly 66 percent of Zolgensma® recipients go on to receive concurrent therapy. This is important to follow, as Zolgensma® does not change the genetic mutation of those being treated with it, so those recipients are still eligible for any therapies that include genetic testing as criteria. SMA and current therapies are important to follow closely, as expanded use approval will lead to additional opportunities for those who thought they were too old to receive Zolgensma®.

What's to Come

Hemophilia is another disease anticipated to have gene therapy treatment options available soon. Treatment will be a one-time IV infusion with a most recently estimated price tag of $3,500,000. The addition of this gene therapy onto formularies isn't an attempt to save lives or slow disease progression, but instead, it offers an alternative to therapies that are already on the market.

For hemophilia, factor replacement products are currently available and recognized as standard of care. The reason these gene therapies are viewed as an alternative is because of the patient-specific degrees of efficacy and because the benefit appears to be temporary. A study published in the New England Journal of Medicine looked at multi-year follow-up data for one of the hemophilia gene therapies. At the end of three years, all of the participants were able to maintain factor VIII levels above what they had been able to do prior to receiving the gene therapy. However, the majority went on to receive factor replacement in some capacity, and most patients were still considered to have moderate hemophilia. Data showed the peak effect within three years and the maximum effect about five years after administration.[5]

Because this gene therapy was an FDA front-runner, after reviewing this data, as well as follow-up data, the FDA created a higher standard for approvals than the traditional protocols in place. This is one of the gene therapies expected to enter the market in 2022.[6]

Limited Use

These new types of therapies require long-term follow-up to generate a comprehensive efficacy profile. While innovative products are exciting in the hope that they provide, they may not always be the best option in the long run.

Gene therapies are currently limited to one-time use per lifetime. This means that if a patient is treated with any gene therapy, they will not be eligible for another gene therapy, even if it treats a different disease. This is primarily because most gene therapies utilize similar adeno-virus vectors to introduce the new codes into the body. The purpose of the inactivated adenovirus is to ensure the product reaches the target cells safely and accurately. However, with viruses, our body develops antibodies against them as a means to be prepared against future exposure, which limits this virus's use for product delivery in the future.

When introducing a new entity into the body, another concern is always a possibility of an immune system attack, since there also is the reality that the virus will not be limited to the intended target cells, potentially causing adverse reactions. This has been seen with CAR T-cell therapies as they attack cancer cells, along with healthy cells that have properties similar to the cancer cells.

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How Can Stop Loss Protection and Cost Containment Efforts Help?

Stop Loss insurance helps to ensure that self-funded employers are protected from the financial impact of high-cost claims related to treatments like gene and cell therapies should covered members receive such treatment. Our specialized Pharmacy Operations (RxOps) team helps to identify potential high-cost claims and predicts the cost impact on plan years by utilizing clinical expertise on medication therapies and disease states. RxOps also provides expert knowledge of cost-containment strategies.

Some general cost-containment recommendations associated with gene and cell therapies include:

- Clearly addressing the use (and limitations) of gene therapy in the plan document
- Knowing your population risk
- Identifying active risks through claims for genetic testing procedures
- Knowing what to expect at the prior authorization or pre-certification level, prior to the plan being billed and product received
- Preparing for potential ancillary expenditures related to the therapy
- Notifying HM Insurance Group if the Health Plan is not covering these items

Pharmacy Focus provides valuable information about pharmaceutical industry developments and their associated costs that can impact the growing claims trend in the self-funded insurance market. Be aware of influences and gain insight into approaches that may help to contain costs. Please share topic suggestions or feedback with **HMPharmacyServices@hmig.com**.

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Sources: [1]"Basics of Gene Therapy," genehome, https://www.thegenehome.com/what-is-gene-therapy, accessed September 1, 2021; [2] "The Multi-Luminance Mobility Test (MLMT) Course," Luxturna® (voretigene neparvovec-rzyl), https://luxturnahcp.com/efficacy/MLMT-clinical-trial/, accessed September 1, 2021; [3]"CAR-T Cell Therapies: How Much for Survival," Association of European Cancer Leagues, https://www.europe-ancancerleagues.org/wp-content/uploads/2018/06/CAR-T-ECL-Article_Final_20062018.pdf, published June 20, 2018, accessed August 20, 2021; [4]"Analysis of 74 CAR-T Therapy Patients Inform a Blue + Prime Future," Sahli, Brett, Prime Insights, Prime Therapeutics, https://www.primetherapeutics.com/en/news/prime-insights/2021-insights/Analysis-of-74-CAR-T-patients-inform-the-future.html, published July 23, 2021, accessed September 1, 2021; [5]"Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A," New England Journal of Medicine, https://www.nejm.org/doi/full/10.1056/nejmoa1908490, published January 2, 2020, accessed September 1, 2021; [6]"Novartis Announces Lift of Partial Clinical Trial Hold and Plans to Initiate a New, Pivotal Phase 3 Study of Intrathecal OAV-101 in Older Patients with SMA," Novartis, https://www.novartis.com/news/media-releases/novartis-announces-lift-partial-clinical-trial-hold-and-plans-initiate-new-pivotal-phase-3-study-intrathecal-oav-101-older-patients-sma, published August 3, 2021, accessed September 1, 2021

MTG-3409 (9/21)